

# INITIAL SYMPTOMATIC PITUITARY METASTASIS IN A PATIENT WITH PROSTATE FOAMY GLAND CARCINOMA: TAILORING SAFE AND EFFECTIVE THERAPY

Marin Prpić<sup>1</sup>, Ana Fröbe<sup>1</sup>, Dijana Zadravec<sup>2</sup>, Leo Pažanin<sup>3</sup>, Blanka Jakšić<sup>1</sup>, Ante Bolanča<sup>1</sup> and Zvonko Kusić<sup>1</sup>

<sup>1</sup>Clinical Department of Oncology and Nuclear Medicine, <sup>2</sup>Department of Diagnostic and Interventional Radiology, <sup>3</sup>Ljudevit Jurak Clinical Department of Pathology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia

**SUMMARY** – Metastases to pituitary gland are unusual and mostly asymptomatic, presenting with local symptoms in one of ten patients, and only 3%-5% of them are of prostate origin. Here we report and evaluate the effectiveness and safety of multimodal treatment in a patient with pituitary metastasis of a prostate foamy gland carcinoma. A 78-year-old male patient presented with blurred vision and headache without a previous history of malignancy. Magnetic resonance imaging scans revealed a large sellar mass, with infiltration of the surrounding structures. Maximal transphenoidal reduction of pituitary metastasis was performed, with a histologic finding of metastatic prostate foamy gland adenocarcinoma. Evaluation of the prostate specific antigen revealed a very high level (1461 ng/mL) and foamy gland carcinoma was found on prostate needle biopsy. The patient received 3D conformal external beam radiotherapy with 6 MV photons to the sellar and parasellar region with a tumor dose of 44 Gy, followed by androgen deprivation therapy. Follow up magnetic resonance imaging done after radiotherapy showed shrinkage of the tumor process, with rapid prostate specific antigen decline to 0.3 ng/mL. The visual function was fully established and headache resolved. On the last follow up 14 months after the diagnosis, the patient was alive and free from clinical signs of disease. Tailored treatment, including limited radiotherapy in a higher palliative dose, in a patient with foamy gland symptomatic pituitary metastatic disease resulted in good local and systemic control of the disease. In older male patients with clinical and/or radiologic characteristics suggestive of metastatic pituitary disease, the prostate specific antigen test should be included as part of the work-up.

**Key words:** *Prostate-specific antigen; Prostatic neoplasms; Radiotherapy; Pituitary neoplasms; Neoplasm metastasis*

## Introduction

Metastases to pituitary gland (PM) are unusual and mostly asymptomatic, with local symptoms present in one of ten patients. Metastases are microscopic and of-

ten undetectable with current imaging techniques<sup>1,2</sup>. Breast and lung cancer account for two-thirds of PM, and other tumor types are sporadically detected, with only 3%-5% of prostate origin<sup>2,3</sup>. Symptomatic PM patients are often diagnosed at an advanced stage, with additional metastatic sites, although cases of solitary PM have been described<sup>1,4</sup>. Also, several very common benign conditions can mimic metastatic carcinoma<sup>4</sup>.

In PM patients, palliative multidisciplinary approach is necessary, with local (surgery ± radiothera-

Correspondence to: *Marin Prpić, MD, PhD*, Clinical Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital Center, Vinogradska c. 20, HR-10000 Zagreb, Croatia  
E-mail: marin.prpic@kbcsm.hr

Received January 26, 2015, accepted May 19, 2015

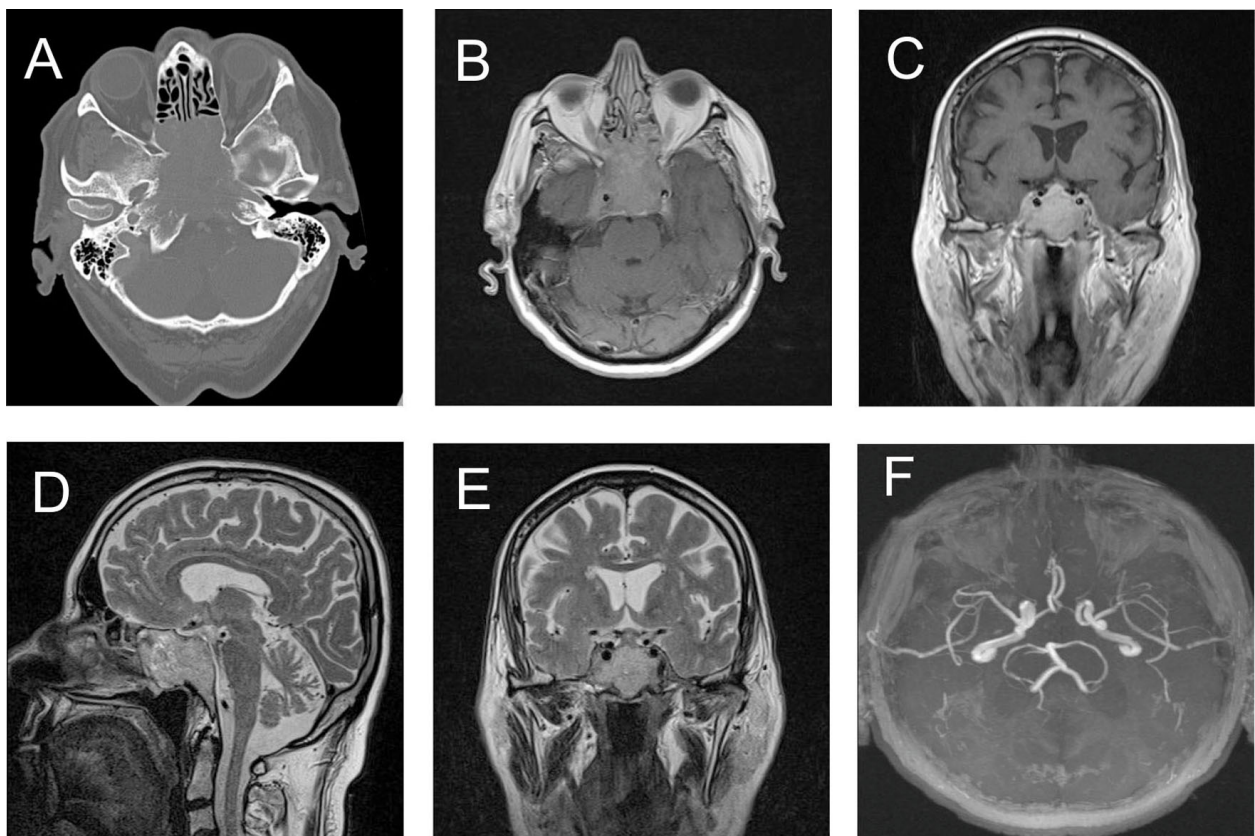
py, RT) and systemic options of treatment (hormonal therapy, chemotherapy, targeted therapies), depending on the primary tumor site and metastatic disease extent<sup>1</sup>. Median survival of PM patients is 6 months, and the majority of these patients will not live long enough to develop specific side effects of treatment. However, in some patients, longer survival was observed, requiring adjustment of treatment strategy<sup>2,5</sup>. Here we report on a patient with symptomatic PM as the first sign of disseminated prostate foamy gland carcinoma, with good treatment response, and discuss optimal palliative treatment strategy and clinical/radiological characteristics of PM.

### Case Report

A 78-year-old Caucasian patient with double and blurred vision, headache, dizziness and nausea, with-

out a previous history of malignancy, was admitted for diagnostic work-up. Magnetic resonance imaging (MRI) scans revealed a large sellar mass, 45x41x33 mm in size, with infiltration of both cavernous sinuses and spreading to the suprasellar cisternal space, optic chiasm, sphenoidal sinus and ethmoid, without brain metastases. Computed tomography (CT) scan showed destruction of the sphenoid sinus walls, posterior part of the ethmoid bone, both perpendicular plates of the palatine bone, clivus, apex of the left and right pyramid, and left medial pterygoid plate. Magnetic resonance angiography 3D time of flight (MRA 3D TOF) showed widening of the circle of Willis and displacement of A1 segment of the anterior cerebral artery (Fig. 1).

The patient did not experience signs of diabetes insipidus. Results of initial endocrinological evaluation are shown in Table 1. Maximal transsphenoidal



*Fig. 1. Preoperative radiographic images: (A) computed tomography scan in bone window; (B) magnetic resonance imaging (MRI)-enhanced T1WI scan in axial plane; (C) MRI-enhanced T1WI in coronal plane; (D) MRI preoperative T2 scan in sagittal plane; (E) MRI-T2 scan in coronal plane; (F) magnetic resonance angiography 3D time of flight.*

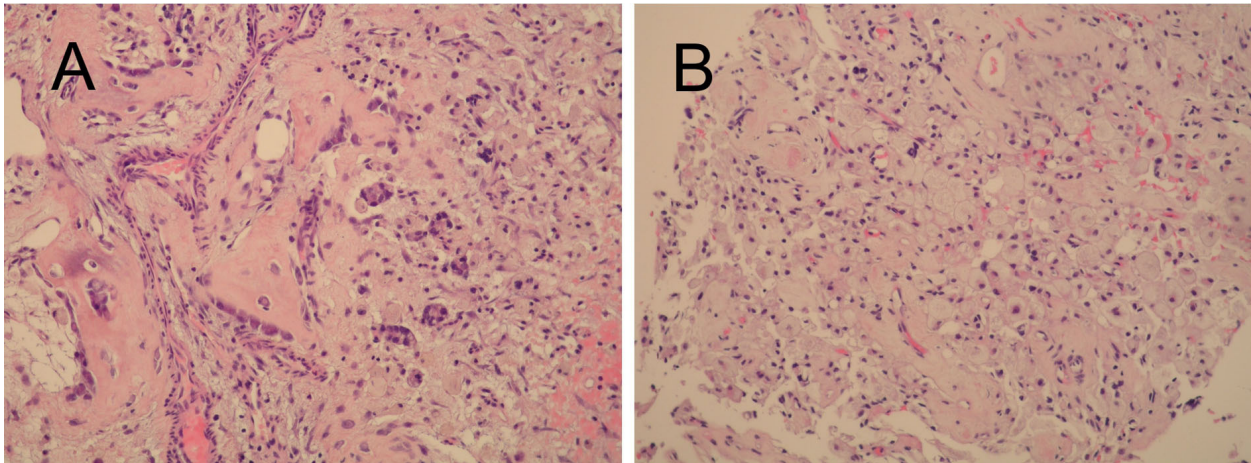


Fig. 2. Histologic examination of removed tissue: (A) pituitary osteoblastic metastasis of the prostatic foamy gland carcinoma (H&E stain, X200); (B) primary tumor site: clusters of foamy gland carcinoma cells in prostatic needle biopsy. (H&E stain, X200)

reduction of PM was performed. Histology specimen of the pituitary tumor showed clusters of foamy cells with small and hyperchromatic nuclei, and minute glandular structures were sporadically formed. Immunohistochemical analysis was performed and the diagnosis of metastatic prostate foamy gland adenocarcinoma was established (Fig. 2). Diagnostic work-up showed a very high prostate specific antigen (PSA) level (1461 ng/mL; reference range: 0-4 ng/mL), and cervical and lumbar spine metastases were detected on bone scan. On prostate needle biopsy, a foamy gland

carcinoma Gleason grade 7 (4+3), histologically similar to the pituitary metastatic tumor, was found. Cancer was found in three of ten cores from both prostate lobes, with maximal 30% core involvement. MRI of the sellar and parasellar region done before radiotherapy showed a residual tumor mass, 27x11 mm in size, with infiltration of the right cavernous sinus.

The patient received 3D-conformal RT with 6 MV photons to the sellar and parasellar region with a tumor dose of 44 Gy in 22 fractions (2.0 Gy/fraction, five times a week). The doses to the organs at risk were 43 Gy, with Dmax 45 Gy to the optic chiasm, and Dmax of 45 and 44 Gy to the optic nerves (left/right). Hormonal therapy with an LH-RH ago-

Table 1. Results of initial endocrinological evaluation

Hormone	Measured level	Reference range (adult men)
LH	13.4 IU/L	1.7-8.6 IU/L
FSH	13.4 IU/L	1.5-12.4 IU/L
TSH	1.02 mIU/L	0.4-4.0 mIU/L
T3	1.27 nmol/L	1.1-3.1 nmol/L
T4	142 nmol/L	60-165 nmol/L
Testosterone	9.8 nmol/L	9.5-28.3 (>50 yrs)
ACTH (8 h)	2.7 pmol/L	7-10 h: 1.6-13.9
Cortisol	788 nmol/L	7-10 h 171-536
		16-20 h 64-327
GH	0.428 ng/mL	<3.0
PRL	73 mIU/L	86-324

LH = luteinizing hormone; FSH = follicle-stimulating hormone; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; ACTH = adrenocorticotropic hormone; GH = human growth hormone; PRL = prolactin

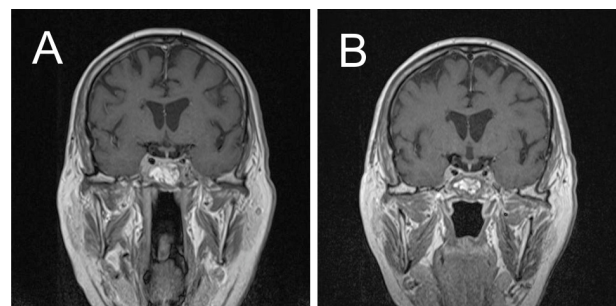


Fig. 3. Follow-up radiographic images (magnetic resonance imaging): (A) early postoperative enhanced T1 in coronal plane (inserted fat in postoperative area); (B) post-radiotherapy enhanced T1 in coronal plane (shrinkage).

nist (leuprolide acetate, 22.5 mg) was introduced with the oral nonsteroidal antiandrogen flutamide, at the beginning of LH-RH therapy to prevent flare or tumor compression to the spinal cord and optic nerves/chiasm. The LH-RH agonist was administered every three months. This therapy resulted in regression of clinical symptoms, with fully recovered visual function and resolution of headache. Follow up MRI done after RT showed shrinkage of the tumor (Fig. 3), while PSA level declined rapidly to 0.3 ng/mL. On the last follow up 14 months after the diagnosis, the patient was alive and free from any clinical signs of the disease.

## Discussion

Pituitary metastases are rarely reported, with data mostly collected from historical autopsy series with only few symptomatic cases reported<sup>4,6</sup>. The most frequent clinical and radiological features of PM, and characteristics of the patient are shown in Table 2<sup>7</sup>. Due to many similar features, PM can be mistaken for a much more common pituitary adenoma, and sometimes only pathological report gives the right diagnosis. However, clinical diagnosis of PM can be made with a combination of diagnostic features. Foamy gland carcinoma is a variant of prostatic acinar adenocarcinoma characterized by abundant, foamy cytoplasm, typically small and hyperchromatic nuclei, and minimal cytologic atypia<sup>8</sup>. Foamy gland carcinoma is mostly admixed with the usual acinar adeno-

carcinoma and the pure foamy gland form is relatively uncommon. This histologic variant of prostatic adenocarcinoma is often associated with indolent clinical behavior, but some patients having cancer with aggressive biological behavior could be classified as an intermediate-grade cancer<sup>9</sup>.

Symptomatic metastatic PM often infiltrates surrounding structures and total removal of the tumor is usually not feasible<sup>2</sup>. Therefore, postoperative palliative RT must be included whenever possible to improve the local control rate. RT can be delivered to a limited (RT to the sellar and parasellar region, to pituitary fossa, and stereotactic RT) or extended area (whole brain RT with/without boost to the pituitary fossa)<sup>10</sup>. A limited radiation field could result in reduction in the grade and severity of side effects, but with the possible higher percentage of treatment failures, while extended radiation could provide eradication of microscopic disease with the burden of toxicity. Synchronous brain parenchyma metastases are not common in PM patients<sup>11</sup>, so whole brain RT could be omitted, especially in patients with smaller tumors.

The maximum radiation dose delivered to the tumor is limited by the surrounding tissue radiation tolerance. The radiation-induced optic neuropathy develops in the time frame of 1-2.5 years<sup>12</sup>. However, some studies have reported that the radiation tolerance threshold could be lower in patients with pituitary tumors *vs.* non-pituitary targets, with complications occurring at low doses of 46 Gy (1.8 Gy/fraction), and Dmax 46 and 45 Gy. The risk of nerve injury was increased with a larger fraction size (>2 Gy), and a median period of latency of only 10.5 months was observed in patients with PM<sup>13-16</sup>. The majority of data on RT to pituitary gland are collected from radiotherapy of pituitary adenomas, administered for tumor mass and hypersecretion reduction, usually at a median total dose >50 Gy in smaller fractions ( $\leq 2$  Gy)<sup>16</sup>. Palliative RT doses to the brain are commonly delivered at a schedule of 30 Gy (3 Gy/fraction, five times a week), and this dose can be sufficient in some patients. However, a schedule of 44 Gy delivered in 2 Gy daily fractions, Dmax of organs at risk, is below the threshold and a higher palliative radiation dose is delivered.

The level of PSA can be elevated, or even within the reference range in metastatic pituitary disease<sup>17</sup>.

Table 2. Clinical and radiological patient characteristics suggestive of metastatic pituitary disease

Clinical characteristics
Diabetes insipidus
Hyperprolactinemia
Optic nerve deficit
Headache
Fatigue
Radiological characteristics
Sellar enhancing mass
Suprasellar enhancing mass
Cavernous sinus invasion
Sellar abnormality
Stalk enhancing

Caution is needed on interpretation because PSA levels can also be elevated in non-prostatic malignant disease<sup>18</sup>. However, highly elevated PSA levels are suggestive of active malignant prostatic disease, and rapid fall of these values to almost undetectable levels could predict good treatment response. Low testosterone level as a result of pituitary dysfunction<sup>19</sup> could work synergistically with LH-RH, and shorten the time to achieve chemical castration. Tailored multimodality treatment, including limited RT at a higher palliative dose, in our patient with foamy gland prostate carcinoma with upfront pituitary metastasis resulted in good local and systemic control of the disease, with minimizing the risk of radiation-induced optic neuropathy. In older male patients with clinical and/or radiological characteristics suggestive of metastatic pituitary disease, the PSA test should be included as part of the work-up.

## References

- Fassett DR, Couldwell WT. Metastases to the pituitary gland. *Neurosurg Focus*. 2004;16(4):1-4.
- Komninos J, Vlassopoulou V, Protopapa D, Korfiatis S, Kontogeorgos G, Sakas DE, et al. Tumors metastatic to the pituitary gland: case report and literature review. *J Clin Endocrinol Metab*. 2004;89:574-80.
- He W, Chen F, Dalm B, Kirby PA, Greenlee JD. Metastatic involvement of the pituitary gland: a systematic review with pooled individual patient data analysis. *Pituitary*. 2014; Jan 21. [Epub ahead of print]
- Famini P, Maya MM, Melmed S. Pituitary magnetic resonance imaging for sellar and parasellar masses: ten-year experience in 2598 patients. *J Clin Endocrinol Metab*. 2011;96(6):1633-41.
- Sioutos P, Yen V, Arbit E. Pituitary gland metastases. *Ann Surg Oncol*. 1996;3:94-9.
- Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol*. 2000;31(5):578-83.
- Max MB, Deck MD, Rottenberg DA. Pituitary metastasis: incidence in cancer patients and clinical differentiation from pituitary adenoma. *Neurology*. 1981;31(8):998-1002.
- Eble JN, Suter G, Epstein JI, Sesterhenn IA. Pathology and genetics of tumours of the urinary system and male genital organs. In: WHO Classification of Tumours. IARC Press; Lyon, 2004.
- Tran TT, Sengupta E, Yang XJ. Prostatic foamy gland carcinoma with aggressive behavior. Clinicopathologic, immunohistochemical, and ultrastructural analysis. *Am J Surg Pathol*. 2001;25(5):618-23.
- Sun DQ, Cheng JJ, Frazier JL, Batra S, Wand G, Kleinberg LR, et al. Treatment of pituitary adenomas using radiosurgery and radiotherapy: a single center experience and review of literature. *Neurosurg Rev*. 2010;34(2):181-9.
- Marsh JC, Garg S, Wendt JA, Gielda BT, Turian JV, Herskovic AM. Intracranial metastatic disease rarely involves the pituitary: retrospective analysis of 935 metastases in 155 patients and review of the literature. *Pituitary*. 2010;13(3):260-5.
- Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation dose-volume effects of optic nerves and chiasm. *Int J Radiat Oncol Biol Phys*. 2010;76(3 Suppl):S28-35.
- van den Bergh AC, Dullaart RP, Hoving MA, Links TP, terWeeme CA, Szabó BG, et al. Radiation optic neuropathy after external beam radiation therapy for acromegaly. *Radiother Oncol*. 2003;68:95-100.
- Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR. Radiation optic neuropathy after megavoltage external-beam irradiation: Analysis of time-dose factors. *Int J Radiat Oncol Biol Phys*. 1994;30:755-63.
- Mackley HB, Reddy CA, Lee SY, Harnisch GA, Mayberg MR, Hamrahian AH, et al. Intensity-modulated radiotherapy for pituitary adenomas: the preliminary report of the Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys*. 2007;67:232-9.
- Rim CH, Yang DS, Park YJ, Yoon WS, Lee JA, Kim CY. Radiotherapy for pituitary adenomas: long-term outcome and complications. *Radiat Oncol J*. 2011;29(3):156-63.
- Lim AC, Cerra C, Pal P, Kearney T, Gnanalingham KK. Visual loss from a pituitary mass: collision tumors of prostatic metastasis and suprasellar meningioma. *J Neurol Surg A Cent Eur Neurosurg*. 2013;74(Suppl 1):e81-4.
- Alanen KA, Kuopio T, Koskinen PJ, Nevalainen TJ. Immunohistochemical labelling for prostate specific antigen in non-prostatic tissues. *Pathol Res Pract*. 1996;192:233-7.
- Tirosh A, Benbassat C, Lifshitz A, Shimon I. Hypopituitarism patterns and prevalence among men with macroprolactinomas. *Pituitary*. 2014; Apr 4. [Epub ahead of print]

## Sažetak

## INICIJALNO OTKRIVENA SIMPTOMATSKA METASTAZA U HIPOFIZU U BOLESNIKA S KARCINOMOM PROSTATE PJENUŠAVIH STANICA: ODREĐIVANJE SIGURNE I EFIKASNE TERAPIJE

M. Prpić, A. Fröbe, D. Zadržavec, L. Pažanin, B. Jakšić, A. Bolanča i Z. Kusić

Metastaze u hipofizu su vrlo rijetke, a oko 3%-5% čine metastaze s ishodištem u prostati, u većini slučajeva su asimptomatske, dok su lokalni simptomi prisutni samo u jednog od deset bolesnika. Ovim slučajem prikazujemo i procjenjujemo učinkovitost i sigurnost multimodalnog liječenja u bolesnika s metastazama u hipofizu primarnog ishodišta u karcinomu prostate pjenušavih stanica. Prikazuje se 78-godišnji muškarac bez prethodne anamneze maligne bolesti kod kojega su se pojavili simptomi zamućenog vida i glavobolje. Magnetskom rezonancom je otkrivena velika selarna masa s infiltracijom okolnih struktura. Učinjena je maksimalna transfenoidna redukcija metastaze u hipofizi te je dobiven histološki nalaz metastatskog adenokarcinoma prostate pjenušavih stanica. Otkrivena je vrlo visoka vrijednost za prostatu specifičnog antigena (1461 ng/mL) te je biopsijom prostate tankom iglom dobiven nalaz karcinoma pjenušavih stanica. Bolesnik je primio 3D-konformalnu radioterapiju vanjskim snopom s fotonima energije 6 MV na selarnu i paraselarnu regiju s tumorskom dozom od 44 Gy te je nastavio primati androgenu deprivacijsku terapiju. Kontrolna snimka magnetske rezonance pokazala je smanjenje tumorskog procesa s brzim padom za prostatu specifičnog antigena na 0,3 ng/mL. Uspostavljena je potpuna vizualna funkcija s postupnim nestankom glavobolje. Na posljednjem kontrolnom pregledu 14 mjeseci nakon postavljene dijagnoze bolesnik je živ, bez kliničkih znakova bolesti. Prilagođeno liječenje bolesnika sa simptomatskom metastatskom bolesti od karcinoma pjenušavih stanica, koje uključuje ograničenu radioterapiju u višoj palijativnoj dozi, rezultiralo je dobrom lokalnom i sistemskom kontrolom bolesti. U starijih muških bolesnika s kliničkim i/ili radiološkim osobinama sa sumnjom za metastatsku bolest u hipofizu test za prostatu specifičnog antigena trebao bi biti uključen kao dio obrade.

Ključne riječi: *Antigen specifičan za prostatu; Prostata, tumori; Radioterapija; Hipofiza, tumori; Tumorska metastaza*